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379,584 Vol 10

From: Canella, Karen
Sent: Sunday, January 20, 2002 1:12 PM
To: STIC-ILL
Subject: ill order 09/802,457

5658043

Art Unit 1642 Location 8E12(mail)

Telephone Number 308-8362

Application Number 09/802,457

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Acta Neurochirurgica 25, 57—68 (1971)

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The Enzyme-Pathobiochemistry of Intracranial Processes

A Contribution

By

P. Oldenkott, W. Heller, H. Blankenhorn, and W. Elies

With 4 Figures

Summary

Enzymes, particularly lactate dehydrogenase (LDH) and its iso-enzymes IV and V, are important in the differentiation of brain tumours. Their values are determined and compared.

In malignant cerebral tumours (glioblastoma multiforme) the enzyme distribution pattern of LDH has been found to be altered. In malignant intracranial tumours, the iso-enzyme V was relatively increased compared with iso-enzyme IV. The difference in the CSF is statistically significant in benign tumours of the interior of the skull (e.g. meningioma, neurinoma, pituitary adenoma), whereas the activities of LDH and its iso-enzymes in the serum show no significant difference in either malignant or benign intracranial processes.

We report our findings at this stage only in the hope of stimulating further studies. Systematic investigations, including control cases, have not yet been concluded.

Zusammenfassung

Ein Beitrag zur Enzym-Pathobiochemie von intrakraniellen Prozessen

Neben anderen Enzymen ist vor allem die Bestimmung und der Vergleich der Lactatdehydrogenase (LDH) und ihrer Isoenzyme IV und V im Serum und im Liquor cerebrospinalis für die Differentialdiagnose von Hirntumoren von Bedeutung.

Es wurde nämlich ein verändertes Enzymverteilungsmuster der LDH bei malignen Hirntumoren (Glioblastoma multiforme) beobachtet. Dabei zeigte sich, daß das Isoenzym V gegenüber dem Isoenzym IV der LDH bei bösartigen intrakraniellen Tumoren quantitativ erhöht ist. Der Unterschied

im Liquor cerebrospinalis ist im Vergleich zu gutartigen Tumoren des Schädelinnenraumes (z. B. Meningeome, Neurinome, Hypophysenadenome) statistisch signifikant, während die Enzymaktivitäten der LDH und ihrer Isoenzyme im Serum bei bösartigen und gutartigen intrakraniellen Prozessen keinen signifikanten Unterschied aufweisen.

Die Mitteilung der eigenen Untersuchungsergebnisse soll zunächst lediglich zur Anregung dienen. Systematische Untersuchungen, die durch Kontrollen vervollständigt werden sollen, sind noch nicht abgeschlossen.

Early diagnosis and suitable treatment of intracranial processes are the most important factors influencing prognosis "quoad vitam et functionem". With the introduction of instrumental methods the exact diagnosis of intracranial processes has become possible but the availability of such facilities is necessatily limited to specialised clinics. Filter stations, out-patient departments, and general hospitals, are of decisive importance for the timely recognition of suspected brain tumours. Therefore, attempts have been made to improve the possibilities of early diagnosis of intracranial processes (Heller et al. 1971).

Within these endeavours, enzyme diagnosis has been more and more developed as an indicator of certain diseases. Lesions of organic tissues, brain tissue included, are known to be associated with the release of certain enzymes. This knowledge was the theoretical starting point of own studies.

Enzyme diagnosis offers three advantages:

1. It is exceedingly sensitive. Even with a minor degree of cell damage an enzyme rise can be observed in the serum.

2. Compared with the serum proteins, the serum enzymes have a very short half-life and thus reflect at all times the actual standing of the pathological process.

3. Enzyme assays are nearly specific. Their primary non-specificity can be largely compensated by comparing the values of two or three enzymes and additionally determining organ-specific enzymes.

Enzyme diagnosis thus permits demonstration of the course of a pathological cell process and rapid recognition of deterioration or improvement (e.g. as a result of therapeutic measures).

Methods

Sera from 54 patients, and sera plus cerebrospinal fluids (CSF) from another 17 patients were pre-operatively examined. The following enzymes were assayed: GOT (glutamate-oxalacetate transaminase), GPT (glutamate-pyruvate transaminase), MDH (malate dehydrogenase), cholinesterase and, in addition, neuraminic acid. Particular attention was paid to LDH (lactate dehydrogenase) and the activities of its isoenzymes I, IV, and V. Iso-enzyme I was only determined in the CSF.

The following discussion is limited to the results concerning serum and CSF LDH and its iso-enzymes. There are two different methods available for the estimation of LDH and its iso-enzymes: The first follows the convention of numbering the five fractions of LDH electrophoretically from I (the most anodic fraction) to V (the most cathodic fraction). The other way is the estimation of LDH and its iso-enzymes spectrophotometrically. By this second method the iso-enzymes are separated into two fractions, the liver type (Iso-enzyme IV) and the heart muscle type (Iso-enzyme V).

Table 1. *Normal Values in the Serum and Cerebrospinal Fluid*

	Serum			Cerebrospinal Fluid (CSF)		
Glutamate-oxalacetate transaminase (GOT)	8	–12	mU	3	— 5,2	mU
Glutamate-pyruvate transaminase (GPT)	8	–12	mU	—		—
Lactate dehydrogenase (LDH)	120	–195	mU	44 ±10 mU		
LDH-Iso-enzyme I	80	–140	mU	7.5 ±0.6 mU		
LDH-Iso-enzyme IV	51.0 ±9 (%)			49.7 ±12 (%)		
LDH-Iso-enzyme V	49.0 ±8 (%)			58.4 ±12 (%)		
Malate dehydrogenase	48	–96	mU	78	–98,5	mU
Cholinesterase	1,900	–3,800	mU	100	–157	mU
Neuraminic acid	20	– 32.5	γ			

Our estimations of lactate dehydrogenase (LDH) were carried out by the latter technique as modified by Bergmeyer and Bernt (1970). It utilises an ultraviolet spectrophotometric apparatus (Boehringer-Mannheim) after separation with DEAE-cellulose. For analysis of the iso-enzyme activities the values before and after treatment with DEAE-Sephadex A 50 in serum and in CSF are measured. By mixing the fluid the LDH-protein of the heart muscle type is bound with Sephadex. In this way the LDH-iso-enzymes of the liver type (the fast moving fractions in electrophoresis) are evaluated directly by the ultraviolet spectrophotometric method, whilst the iso-enzymes of the heart muscle type (the slow moving fractions) are determined indirectly (1).

Normal values were determined from standardised normal sera and control cerebrospinal fluids (2) and they were compared with those reported in the literature. With regard to a normal distribution of the LDH-iso-enzymes IV and V only very few controversial results have been reported. Normal values were derived from 150 tests on sera and compared with the activities of tumour patients (Tab. 1).

Size, localisation and histology of the tumours were taken into

consideration as were internal diseases and therapeutic measures (e.g. administration of hormones, cytostatic agents, anticonvulsants, plasma expanders, blood transfusions, radiation therapy).

Notes: (1) Biochemica Test Combinations (1970);
(2) Hyland Spinal Fluid, Control, Dried.

Table 2. *Serum Enzyme Activities (Mean Values) of 54 Patients*

Intracranial Lesions	Cases	GOT	GPT	LDH	LDH-IV	LDH-V	MDH
Multiform glio-blastoma	3	16.1	8.2	*219.0*	32.7	67.3	44.3
Meningeoma	9	16.4	11.4	121.9	45.0	54.9	49.1
Acoustic neurinoma	6	10.0	7.9	148.9	36.9	63.2	53.5
Chromophobe adenoma	7	7.8	6.5	147.5	34.1	65.9	61.2
Astrocytoma							
KERNOHAN I–II	4	11.8	7.9	158.0	45.0	54.9	65.8
KERNOHAN III–IV	4	14.3	10.7	132.0	35.6	64.4	66.8
Metastasis	1	7.4	7.4	153.0	39.0	61.0	66.0
Inflammatory processes	3	15.1	11.0	143.5	29.0	71.0	82.9
Aneurysm	2	17.6	8.9	*316.0*	40.5	59.5	70.4
Primary hemorrhage							
epidural	1	66.3	12.9	*242.3*	46.9	53.0	*129.5*
subarachnoid	2	7.9	5.6	116.0	38.2	61.9	37.2
Hemangio-blastoma	5	11.9	12.6	151.4	41.3	58.7	68.1
Other lesions	7	12.8	14.7	170.6	47.2	52.8	74.4

Results

The *total serum LDH* was in our own cases, with few exceptions (Tab. 2), in the normal range, on average between 120–195 mU (Tab. 1). Malignant intracranial tumours were associated with a change in the LDH-iso-enzyme pattern, the ratio between iso-enzyme IV and iso-enzyme V having been shifted in favour of the fraction V. Corresponding examinations have generally shown the LDH-iso-enzyme V to be increased in this disease group.

The total LDH is diagnostically less significant than the ratio and percentage rates of its iso-enzymes IV and V. Difficulties also arise in comparisons of glioblastoma and inflammatory processes (Fig. 1). Many authors therefore believe that in malignant processes the pattern of enzyme distribution represents an inflammatory spectrum in the plasma (Goldman et al. 1964 and Wroblewski 1959).

A comparison, of the LDH-enzyme, activities in the serum in glioblastoma, astrocytoma degrees I–II and astrocytoma degrees III–IV according to Kernohan, shows for glioblastoma the highest values in

diseases and therapeutic measures
, cytostatic agents, anticonvulsants,
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Control, Dried.

ities (Mean Values) of 54 Patients

GPT	LDH	LDH-IV	LDH-V	MDH
8.2	*219.0*	32.7	67.3	44.3
11.4	121.9	45.0	54.9	49.1
7.9	148.9	36.9	63.2	53.5
6.5	147.5	34.1	65.9	61.2
7.9	158.0	45.0	54.9	65.8
10.7	132.0	35.6	64.4	66.8
7.4	153.0	39.0	61.0	66.0
11.0	143.5	29.0	71.0	82.9
8.9	*316.0*	40.5	59.5	70.4
12.9	*242.3*	46.9	53.0	*129.5*
5.6	116.0	38.2	61.9	37.2
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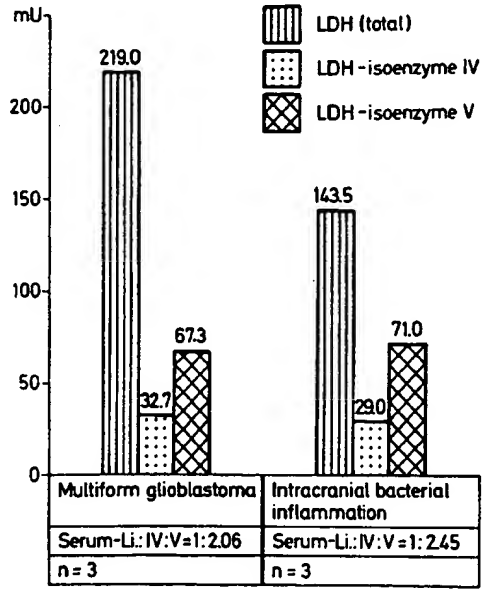

Fig. 1. Comparison of LDH-enzyme activities in the sera in glioblastoma multiforme (3) and inflammatory intracranial processes (3). Serum-LI = Serum LDH-iso-enzyme.

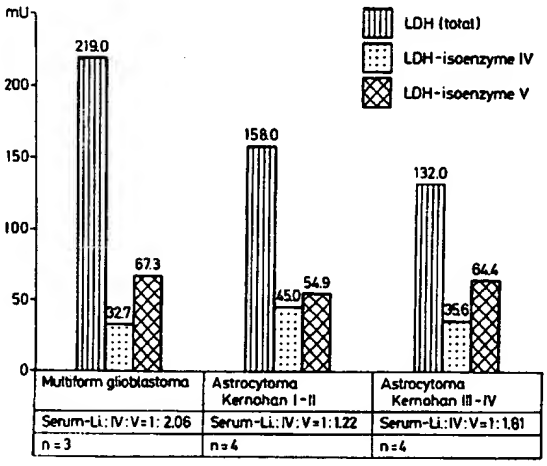

Fig. 2. Comparison of LDH-enzyme activities in the sera in glioblastoma multiforme (3), astrocytoma degrees I and II (4) and astrocytoma degrees III and IV (4). Serum-LI = Serum LDH-iso-enzyme.

the case of iso-enzyme V = 67.3 (Fig. 2). The ratio between the iso-enzymes IV (32.7) and V (67.3) is distinctly shifted in favour of V, the quotient being 1 : 2.06. For astrocytoma degrees I and II the values are 45.0 and 54.9 (1 : 1.22) and for astrocytoma degrees III and IV 35.6 and 64.4 (1 : 1.81). Glioblastoma multiforme and astrocytoma are histologically differentiated.

The LDH activity in the crebrospinal fluid (CSF) is relatively independent of the LDH changes in the serum. This can be ascribed to

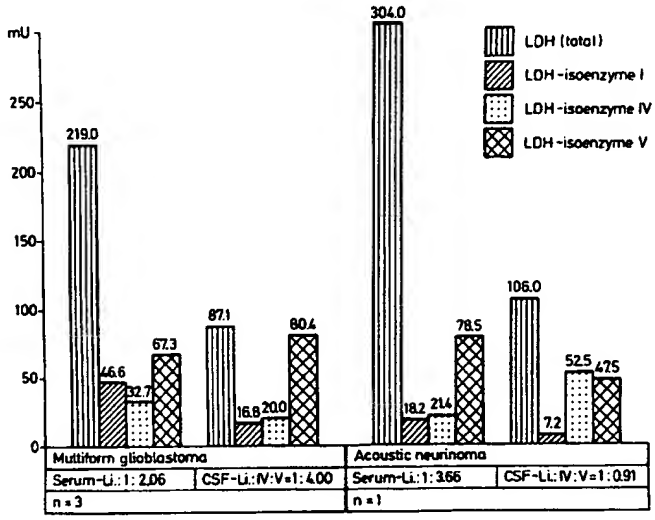

Fig. 3. Comparison of the enzyme activities in the sera and cerebrospinal fluids in glioblastoma multiforme (3) and neurinoma of the acoustic nerve (1). Serum-LI = Serum LDH-iso-enzyme. CSF-LI = CSF-iso-enzyme.

the blood/brain barrier which is impervious to pathological enzyem increases.

The diagnostic information increases when *serum and CSF LDH* are compared. The relation between the total LDH values does not permit a definite conclusion to be drawn with regard to the presence of a malignant intracranial process. Tumours which are usually benign, such as neurinoma of the acoustic nerve, meningioma and pituitary adenoma, may be connected with the same or a similar enzyme distribution (Sano et al. 1965). An altered LDH pattern in the CSF is however strongly suggestive of malignancy (Gerhardt et al. 1967). In the opinion of these authors, the histological degree of malignancy corresponds to the degree of deviation of the iso-enzyme distribution.

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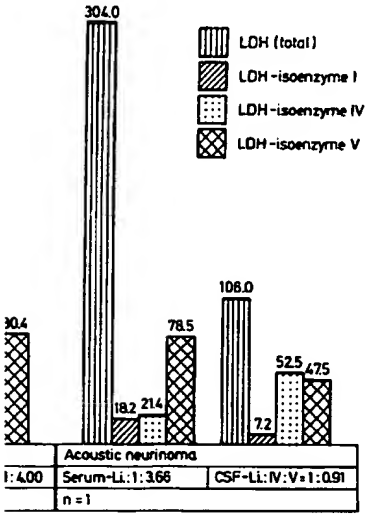

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Gerhardt et al. observed in their patients a decrease of iso-enzyme I and a marked rise of the iso-enzymes IV and V.

Our own examinations largely confirm these data. The relation between the iso-enzymes IV and V, of 1 : 2.06 in the serum, is shifted even more clearly in favour of iso-enzyme V in the CSF. Whereas the CSF total LDH of 87.1 is high, the values for iso-enzyme IV are 20.0, for iso-enzyme V 80.4, the quotient 1 : 4.00.

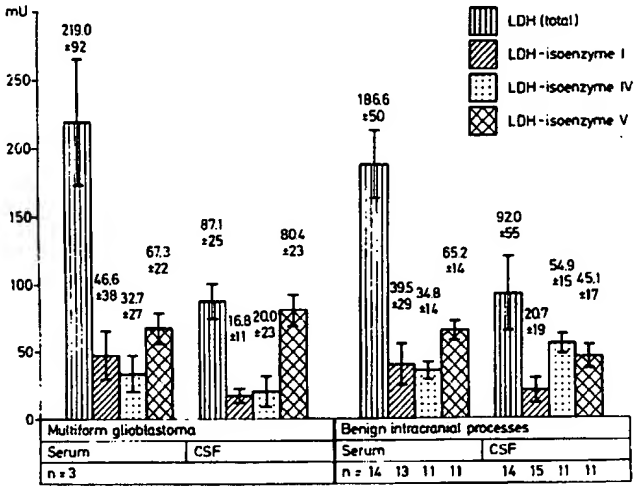

Fig. 4. Comparison of malignant (glioblastoma multiforme) and benign intracranial tumours. (Calculation of significance by the T-test. n = number of patients, $\bar{x}$ = mean value, $\pm s\bar{x}$ = mean standard deviation, P = probable significance.)

A patient with a neurinoma of the acoustic nerve had the total LDH increased (304 mU) and also the iso-enzyme distribution in the serum. According to the quotient of 1 : 3.66 (Fig. 3) the presence of a malignant tumour might have seemed probable, but the CSF-enzyme analysis was contradictory. The CSF ratio iso-enzyme IV (52.5) to iso-enzyme V (47.5) was 1 : 0.91 (Fig. 3).

Thus, from the serum enzyme values alone it is not possible to draw a conclusion with regard to malignancy of an intracranial process. A comparative serum/CSF analysis is indispensable for a distinction between benign and malignant brain tumours. This finding is more impressively demonstrated by a comparison of glioblastomas and patients with benign tumours (Fig. 4). Since there were no significant differences, it was possible to classify different conditions, e.g. patients

with meningioma, pituitary adenoma or neurinoma of the acoustic nerve, as a group with similar LDH-iso-enzyme patterns. Another characteristic of this group is that these processes are histologically benign.

In glioblastoma, the decrease of the LDH-iso-enzyme IV in the CSF and the increase of LDH-iso-enzyme V are statistically significant, compared with the group of benign tumours. No significant difference is present between the serum enzyme activities.

Discussion

The behaviour of LDH in carcinoma patients has been the subject of various studies. Sano et al. (1965) reported that the activities of GOT, GPT, and LDH in the serum and cerebrospinal fluid tended to increase in malignant gliomas but not in benign tumours. However, the increases in enzyme activity were so variable that they could not be utilized as a means of diagnosis in particular cases.

Hill et al. (1954) found in carcinoma patients an increased LDH activity in the serum and no change in benign tumours. Goldman et al. (1964) detected a rise in serum LDH only in about 40–60% of similar cases.

Enzyme diagnosis of brain tumours has met with several difficulties. Serum and CSF enzyme activity estimation in cases of brain tumour have often yielded contraversial results and this has prompted further investigation. For this purpose it is necessary to refer to the following findings.

In our cases a quantitative rise in total LDH was found in 2 cases of cerebral aneurysm. There was no significant shift of the iso-enzyme fractions (Tab. 2). Weissmann (1959) observed in 6 cases of cerebral aneurysm increased LDH and SGOT values of unclarified actiology. The LDH increase might be explainable by subarachnoid haemorrhage since the pattern of enzyme distribution in the serum is typical of haemolysis (increased GOT and MDH values but normal GPT activity).

In a patient with epidural haematoma and severe muscular trauma (Tab. 2) the increase in GOT, LDH, and MDH values in the serum can be interpreted as a result of muscular trauma and intravascular haemolysis. This view is supported by the fact that the level of SGPT, which is almost absent in skeletal muscle and erythrocytes, was not raised.

The increase of total LDH in a patient with an ependymoma of the 4th ventricle is unexplained.

The high serum total LDH value in a patient with a neurinoma (Tab. 3) is possibly due to haemolysis since serum GOT and MDH are also raised.

The characteristic feature of the behaviour of LDH in carcinoma patients is that total LDH values are not necessarily increased, the essential observation being shift within the iso-enzyme distribution. Riley (1960) carried out experimental studies to investigate the cause of the iso-enzyme shift. An isolated transfer of whole blood or plasma or organic extracts from mice with cancer to healthy animals was followed after 48 hours by a rise in serum LDH in the recipients. Riley et al. ascribed this rise to an as yet undefined factor which probably originates from the largely glycolytic tumour cells. It is interesting that in tumour cells there is an LDH which is probably of a different variety to the LDH in healthy cells.

Richterich et al. (1962) claim that total LDH in serum and exudates is only of limited diagnostic importance in malignant tumours. In their opinion iso-enzyme analysis enables a differentiation to be made between benign and malignant tumours.

Buckell et al. (1970) analyzed the cerebral cyst fluid of 100 patients with histologically verified brain tumours. They estimated the total LDH and separated the five fractions of this enzyme by an electrophoretical method. Their results fell into two main groups (Tab. 4).

Fluids from malignant tumours had the highest total activity of LDH and more than 10% of the activity was due to LDH V.

Fluids from benign tumours had a lower total LDH, less than 10% being of LDH V.

Secondary carcinomas were most active and the highest LDH levels were associated with frequent mitoses and anaplasia. Astrocytomas grades III and IV were very similar to each other and to the less active secondaries, contrasting strongly with astrocytomas grades I and II.

Fluids from hemangioblastomas, chromophobe pituitary adenomas, and neurilemomas had low levels of total LDH activity, and little or no LDH V.

In our studies it was found that comparison of LDH-iso-enzymes in serum and CSF is important for differentiation between malignant and benign intracranial tumours. In glioblastoma, for example, the total serum LDH should be increased only slightly or not at all but the iso-enzyme pattern is frequently altered. The comparison of glioblastoma with other benign intracranial processes in Fig. 4 shows this clearly. The relation between the iso-enzymes IV and V is shifted in favour of iso-enzyme V. The LDH iso-enzyme IV to LDH iso-enzyme V quotient in CSF in glioblastoma is 1 : 4 and in the other intracranial processes 1.22 : 1. In glioblastoma, in contrast to the activities of LDH and its iso-enzymes in the serum, the change is statistically significant at 0.01.

Comparing astrocytoma I to II, astrocytoma III to IV (Kernohan), and glioblastoma multiforme for their iso-enzyme distributions in serum,

Table 3. *Enzyme Activities in the Sera and Cerebrospinal Fluids of 6 Patients*

Intracranial Lesions	Cases	GOT	GPT	LDH	LDH-I	LDH-IV	LDH-V	MDH	ChE
Multiform Glioblastoma	3								
a) Serum		16.1	8.2	219.0	46.6	32.7	67.3	44.3	1463
b) CSF		—	—	87.1	16.8	20.0	80.4	—	—
Acoustic Neurinoma	1								
a) Serum		21.2	9.7	304.0	18.2	21.4	78.5	118.0	1710
b) CSF		6.9	—	106.0	7.2	52.5	47.5	22.6	82
Meningeoma	2								
a) Serum		14.9	10.4	130.1	17.2	32.5	67.5	67.0	2455
b) CSF		12.6	—	45.8	3.6	—	—	24.8	93

b) CSF		—	—	87.1	16.8	20.0	80.4	—	—
Acoustic Neurinoma	1								
a) Serum		21.2	9.7	304.0	18.2	21.4	78.5	118.0	1710
b) CSF		6.9	—	106.0	7.2	52.5	47.5	22.6	82
Meningeoma	2								
a) Serum		14.9	10.4	130.1	17.2	32.5	67.5	67.0	2455
b) CSF		12.6	—	45.8	3.6	—	—	24.8	93

Table 4. *Ranges and Mean Values of Lactate Dehydrogenase Activities Found in the Fluids from Different Types of Cystic Intracranial tumors* (J. Neurosurg. *32* [1970] p. 547)

Tumor Type	No. of Cases	Total LDH (in per liter)	LDH-iso-enzymes (%)				
			1	2	3	4	5
Secondary carcinoma	20	10,090 (380–29,300) SD 8523	8 (0–18) SD 5. 6	16 (0–29) SD 7. 4	23 (11–35) SD 5. 9	26 (17–37) SD 4. 8	27 (9–58) SD 13. 8
Astrocytoma grade IV	12	3,504 (550–8,200) SD 2638	14 (1–45) SD 12. 1	24 (12–40) SD 9. 5	24 (12–32) SD 5. 3	19 (2–26) SD 8. 3	19 (2–31) SD 9. 8
Astrocytoma grade III	32	3,170 (226–8,640) SD 2477	18 (1–68) SD 14. 7	24 (10–34) SD 4. 7	24 (7–34) SD 5. 0	18 (0–28) SD 7. 1	16 (0–26) SD 6. 8
Astrocytoma grade II	3	383 (240–600)	28 (13–49)	30 (23–35)	24 (16–31)	11 (2–19)	7 (0–20)
Astrocytoma grade I	5	168 (85–267)	37 (0–49)	33 (16–41)	21 (9–37)	9 (0–47)	0 0
Hemangioblastoma	9	210 (110–387)	46 (26–77)	37 (23–50)	15 (0–33)	1.8 (0–13)	0.2 (0–7)
Chromophobe adenoma	4	589 (140–1,055)	34 (21–50)	36 (30–41)	23 (11–32)	6 (1–11)	1 (0–2)
Craniopharyngioma	2	2,500 2,000 & 3,000	10 2 & 18	17 13 & 21	14 4 & 23	22 19 & 25	37 37 & 38
Neurilemoma	5	160 (100–240)	48 (38–75)	33 (13–48)	15 (16–21)	3 (0–6)	1 (0–3)

it is seen that, as the degree of malignancy of the tumour increases so does the quantity of iso-enzyme V (Fig. 2). Thus, a relationship between the iso-enzyme quotient and the degree of malignancy of a tumour appears possible. A quotient of less than 1 should always call for further investigation.

The problem of an exact serum analysis is that superimposition of the patterns of various enzymes makes it difficult to locate the organ concerned. This difficulty is eliminated by comparing serum and CSF values. Atypical enzyme patterns are to be expected when the cellular and enzymatic composition of the organ of origin has undergone pathological change.

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